

Agents and Cancer Development

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Abstract

Population (epidemiological) and laboratory studies have led to the discovery of many potential environmental factors in the initiation, promotion and progression of cancer. Starting with Pott's observations in the 18th century, certain occupations have been associated with an increased risk of cancer development. The recognition of increased scrotal cancer in chimney sweeps due to coal and tar exposure was followed by an observation in a British factory that all men distilling 2-naphthylamine developed bladder cancer.

Keywords: Agents, Cancer Development, Drugs.

Introduction

There have also been associations made between different geographical regions and particular cancers. Stomach cancer is 5-6 times higher among Japanese men, attributed to the consumption of fermented foods; breast cancer is 20 times higher among American women, attributed to the high fat American diet; and liver cancer is 10 times higher in Africa, which correlates with high rates of Hepatitis B infection. 4Liver cancer may also be caused by aflatoxin, a food contaminant produced by fungi. This compound is prevalent in grain stores in tropical and subtropical regions because moist grain is a very good place for the fungi to live.

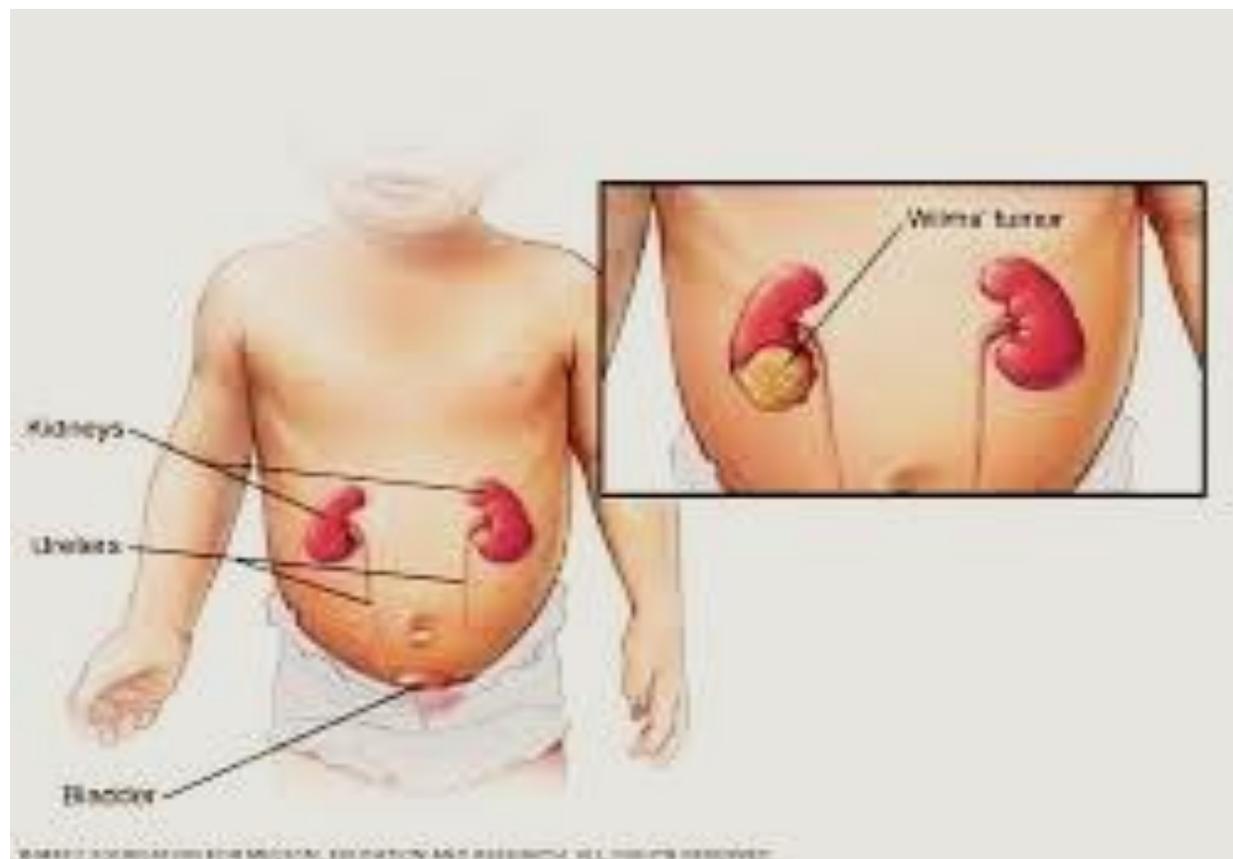
Lifestyle

The impact of many environmental factors can be reduced by making healthy lifestyle choices. One of the most potent carcinogens in humans is benzo[a]-pyrene, a compound found in cigarette smoke. 2In fact, the tar in cigarette smoke includes both initiators and promoters, making it especially dangerous. Alcohol is a promoter of carcinogenesis in humans, as is asbestos. Additionally, UV radiation, from exposure to the sun or tanning beds, is a powerful initiator in humans and is a cause of skin cancer.

Drugs

Tamoxifen, a chemotherapeutic agent used to combat estrogen receptor positive (ER+) breast cancer, increases the risk of endometrial cancer by increasing the rate of endometrial cell proliferation. For this reason, long-term tamoxifen treatment is losing popularity in favor of aromatase inhibitors.6Estrogens themselves may also be important in the promotion of tumors, particularly in post-menopausal women receiving exogenous estrogens, due to their ability to increase mammary and endometrial cell division rates.7This is an area of active research.

There are factors that can predispose an unborn fetus to developing cancer later in life. These include exposure to radiation or the synthetic estrogen diethylstilbestrol (DES).



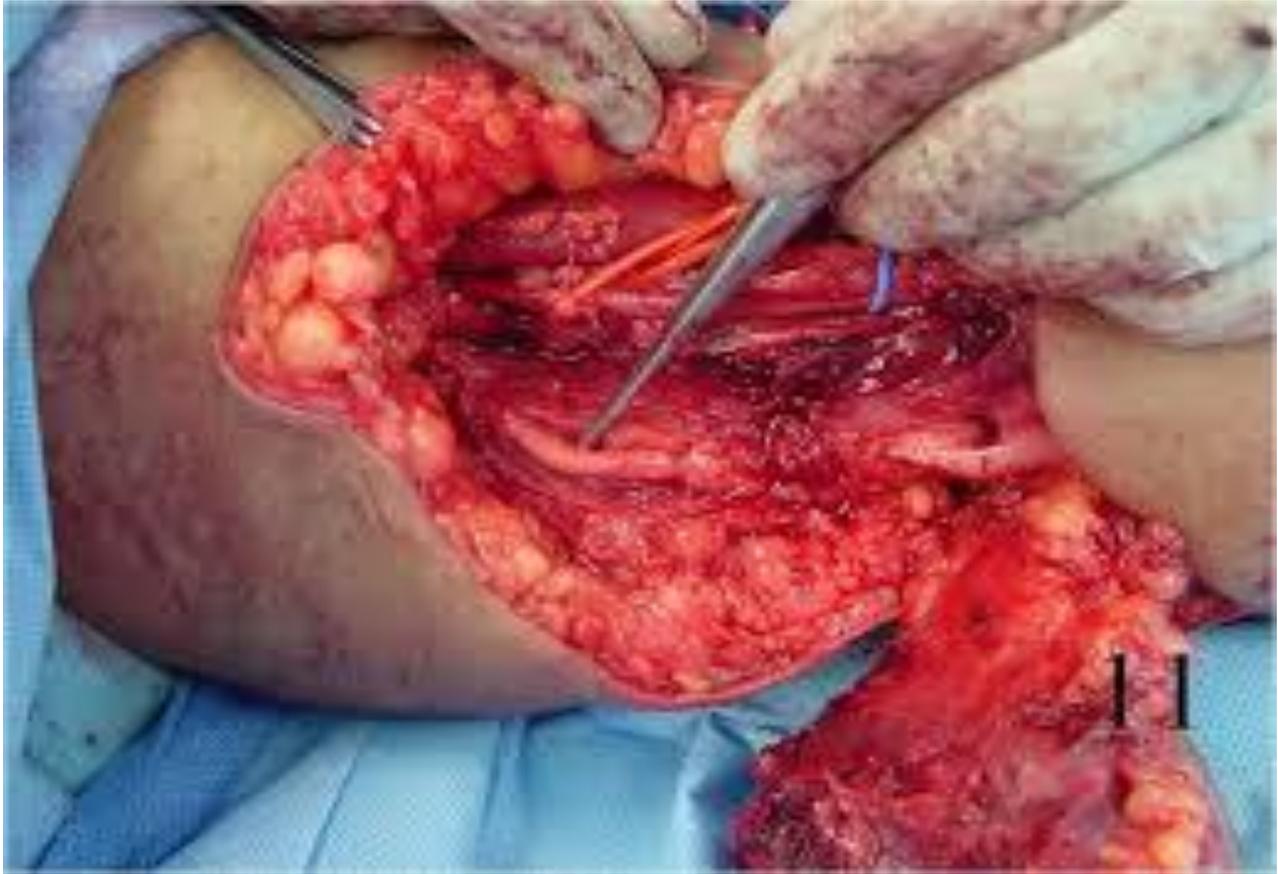
A Closer Look at Aflatoxin: Physical Impact and Associated Cancer

Exposure: Aflatoxin is produced by *Aspergillus flavus* and *Aspergillus parasiticus* fungi. The fungi synthesize aflatoxin when they are living in warm, moist conditions. These fungi are prevalent among crops such as rice, corn, cassava, nuts, peanuts, chilies, and spices. Countries with the highest amounts of these organisms lie within 40 degrees latitude north or south of the equator. Storage of food under warm, moist conditions increases the risk of aflatoxin contamination. Approximately 4.5 billion persons living in developing countries are chronically exposed to uncontrolled amounts of aflatoxin.⁹

Associated Cancer: Aflatoxicosis is the disease that results from ingestion of aflatoxin. This disease can present in one of two forms. The first is an acute illness that results from exposure to large amounts of the toxin over a short period of time. Adult humans have a high tolerance for aflatoxin. Ingestion of large amounts of aflatoxin usually causes liver damage and acute illness but is rarely fatal. However, exposure to high levels of the toxin can cause death in children. The second form of aflatoxicosis is due to low level chronic exposure to aflatoxin. Chronic aflatoxin exposure has an additive effect and can lead to the development of liver cancer. Aflatoxin increases the risk of liver cancer (usually in the form of hepatocellular carcinoma or HCC) in all persons who ingest contaminated food. It can also increase the risk of lung cancer in workers who handle the grain. Infection with either the Hepatitis B or C viruses combined with exposure to aflatoxin can increase a person's risk of developing liver cancer by as much as 30 fold over a person who is exposed to aflatoxin but is not infected with hepatitis virus. Infection with the Hepatitis B virus decreases a person's ability to detoxify aflatoxin via the liver. This can partially account for the greatly increased risk of cancer development in individuals exposed to both aflatoxin and hepatitis virus.⁹

In its initial stages, HCC causes no noticeable symptoms. It can grow for up to 3 years before causing physical symptoms.¹⁰ For this reason, most HCC patients present with advanced stages of the disease, making treatment difficult. Non surgical treatments are only minimally effective. HCC patients have shown to have, at best, a 25%

response rate to chemotherapy, as most HCC tumors are resistant to chemotherapy. Liver transplantation is the only current cure for HCC. Unfortunately, based on the number, size, location, and severity of the underlying disease, not all patients are candidates for a transplant.



Approximately 35% of men, 40% of women, and 17% of youth (ages 2-19) in the United States are obese (based on BMI), according to articles published by the Journal of the American Medical Association in 2016 2829. Since 2005, there has been a slight increase in obesity in women, and the rates in men and children have remained about the same. Even in the face of large amounts of research, new drugs, and community programs to fight weight gain 30, America collectively struggles to slim down.

The evidence for the obesity-cancer connection is growing as thick as America's waistline; more and more research shows that being obese puts people at a greater risk of developing cancer. Solid cancers associated with obesity include: colon, breast (post-menopausal), uterus, pancreas, gallbladder, liver, esophagus, kidney 31, thyroid, and ovaries. Risk is also increased for blood cell cancers, including myeloma, leukemia, and non-Hodgkin's lymphoma 32

Obesity, the Microbiome, and Cancer Risk

The microbiome is the collective genes found in the hundreds of species of bacteria living inside a person. Microbiome changes have been identified as another link between obesity and cancer. The bacteria living inside the gut are usually helpful; they break down and ferment foods and hard-to-digest fibers 54, and they produce important nutrients such as biotin, vitamin K, and vitamin B12 55.

Lean and obese individuals have different mixtures of bacteria in their guts. Slimmer, healthier individuals tend to have lots of different kinds of bacteria, while obese individuals have less diversity 56. Low bacterial diversity has also been associated with insulin resistance, abnormal blood lipid content (dyslipidemia), and inflammation 57. The bacterial community seems to specialize itself depending on the diet being consumed 56. Differences in relative

numbers of different kinds of microbes have been found between people with high-fat “Western” diets, plant-rich diets, or animal protein-rich diets 57.

Why does this matter? Each type of bacteria produces distinctive products (metabolites), and these can be either good or bad for one’s health. Obesity and a high-fat diet are associated with gut permeability and increases in the blood levels of bacterial lipopolysaccharides (LPS). LPS is found in the membranes of some bacteria, including *E. coli* 56. It is a type of toxin, and when LPS binds to its receptors (specifically, Toll-like receptor 4; TLR4)58, it can trigger an immune response by causing the release of pro-inflammatory factors such as TNF- α , interleukin 1 (IL-1), and interleukin 6 (IL-6) 56. This chronic inflammation can fuel tumorigenesis 55. LPS in the blood have also been linked to weight gain, hyperglycemia, and insulin resistance 58.

A recent study in mice (still to be validated in humans) suggests another mechanism by which the microbiome can lead to obesity and insulin resistance. Mice fed a high-fat diet had increased blood levels of acetate, which was later shown to be produced by their intestinal bacteria. This acetate would stimulate the parasympathetic nervous system, which would signal to beta-cells in the pancreas via the vagus nerve to secrete more insulin. They found that acetate also led to increased production of ghrelin, which is a “hunger hormone” that encourages a big appetite. The combination of a hearty appetite (because of too much ghrelin) and increased energy storage (because of too much insulin) is a recipe for obesity and insulin resistance 59.

To make matters worse, the types of bacteria seen in obese individuals has also been shown to be better at extracting energy or calories from food, and this can lead to further weight gain, metabolic dysregulation, and altered adipokine function 55.

Obesity and Chemotherapy

Not only does obesity increase the likelihood of developing cancer, but it can also decrease the effectiveness of some cancer treatments, including chemotherapy, targeted therapy, and anti-angiogenic therapy 60.

Bevacizumab, an anti-angiogenesis drug that prevents tumors from growing a blood supply, is used in combination with conventional chemotherapy to extend colorectal patient survival. A study published in the journal *Gut* suggests that visceral fat (the fat stored around the internal organs in the abdominal cavity) could be used to predict response to this bevacizumab-based therapy; more visceral fat means more tumor progression 61. The researchers think that the extra VEGF (the molecule that bevacizumab inhibits) secreted by visceral fat decreases the effectiveness of the bevacizumab.

Another retrospective study found that obese women with breast cancer developed earlier metastases and had less successful response to first-line chemo treatment with paclitaxel than non-obese women 62. Other researchers found that Chinese breast cancer patients with a higher BMI were less likely to achieve pathological complete response (defined as the absence invasive carcinoma in breast tissue and lymph nodes of in biopsy) after paclitaxel and carboplatin treatment than patients with a lower BMI 63.

Researchers found that in mouse models of pancreatic ductal carcinoma, obesity impaired the delivery and efficacy of chemotherapy drugs by decreasing vascular perfusion 64. Vascular perfusion refers to the extent of blood vessels within a tissue and the resulting delivery of nutrients (or drugs) through the bloodstream. They found that more adipocytes meant more pro-inflammatory cytokines and infiltration by tumor-associated neutrophils. This obesity-associated inflammation was coupled with desmoplasia, the growth of dense, fibrous tissue. Desmoplasia makes it easier for cancer cells to spread 65) and more difficult for blood vessels to grow properly; thus, obesity-induced desmoplasia makes it more difficult for cancer drugs to affect a tumor.

Still another study showed that the high levels of insulin often found in obese patients could activate a pathway (the PI3K/Akt pathway) that makes colon cancer cells more resistant to the chemotherapy drug, oxaliplatin 66. In fact, of current research interest is the benefit of metformin for cancer patients 60. Metformin is an anti-diabetic drug that improves insulin sensitivity, but it has also been shown to improve treatment outcomes and survival in diabetic cancer patients. In addition, metformin has been shown to reduce metastasis in animal models of pancreatic cancer. Metformin may help by inhibiting the production of inflammatory molecules and by reducing desmoplasia 60.

The large-scale clinical trials needed to determine drug dosages for obese patients have not been conducted, and there is little information available to help clinicians understand the drug dynamics of anticancer agents in obese

patients 67. A 2012 report from the American Society of Clinical Oncology (ASCO) noted that up to 40% of obese cancer patients receive inadequate doses of chemotherapy 67. This could lead to an increased likelihood of remission and mortality 68. Drug doses are generally determined based on body surface area, which is calculated using a patient's height and weight 68. This calculation can lead to some extraordinarily high-sounding doses of chemo for larger patients. Some physicians may base a patient's dosage on their ideal body weight or an adjusted body weight, they may cap off the dose at a certain limit, or they may lower the dose due to fear of toxic side effects 69. These fears, however, are unfounded; there is no evidence for additional toxic effects from the high dosages calculated by using a patient's actual body weight 68,69,67. ASCO recommends that physicians should view obese and normal-weight patients equally in terms of chemotherapy dosages with exceptions for the maximums set on the use of carboplatin, bleomycin, and vincristine 67.

Chronic Inflammation and Cancer Development

Chronic inflammation has been seen, both experimentally and epidemiologically, to be an important factor in tumor development. Chronic inflammation can be caused by viral or bacterial infections, autoimmune diseases and inflammatory conditions of unknown origins. It has been shown that mutation of key inflammatory control genes is associated with a higher risk of cancer progression, and markers of inflammation correlate with a worse prognosis for cancer patients. Inflammation seems to lead to the development of cancer because of the activities of leukocytes, including the production of proteins that alter the behavior of target cells (cytokines and chemokines), stimulation of blood vessel growth (angiogenesis) and tissue remodeling. Immune cells also produce oxygen radicals that can cause mutations in DNA.

Inflammation can both induce carcinogenesis and lead to progression and metastasis. The activation of a specific transcription factor, NF- κ B, by pro-inflammatory cytokines has been shown to produce a more aggressive cancer phenotype including resistance to normal growth control mechanisms, angiogenic capability and metastasis. Tumor associated macrophages (TAM), are also associated with the inflammatory pathway, have been observed to produce pro-angiogenic factors and recruit blood vessels early in tumor development. TAM also increase the growth rate of tumor cells and cause the dissolution of the connective tissue matrix surrounding the tumor, enabling tumor growth and spread.

There are several cancer types associated with chronic inflammatory conditions, including; colon cancer and inflammatory bowel disease, liver cancer and hepatitis C, bladder or colon cancer and schistosomiasis (a chronic parasitic infection) and stomach cancer and *H. pylori* infection.

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